Pharmaspire

RESEARCH ARTICLE

In silico studies on *Urtica dioica* as aldose reductase inhibitors

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ABSTRACT

Urtica dioica L. is a perennial plant which is commonly known as "stinging nettle." It is widely distributed throughout the temperate and tropical areas around the world. The genus *Urtica* is derived from word "uro" which means to burn or "urere" which means to sting. Due to the fact that the plant typically either has male or female blooms, the species name is *dioica* which means "two households". Apart from various traditional uses, it is reported for the treatment of diabetes. Owing to the antioxidant potential and presence of flavonoids, here in this research, *in silico* studies has been performed on *U. dioica* to establish its target affinity against aldose reductase.

KEY WORDS: Aldose reductase, Diabetic complications, Molecular docking, *Urtica dioica*

INTRODUCTION

Urtica dioica L. is a perennial plant which is commonly known as "Stinging nettle." The active chemical part of nettle includes nearly fifty compounds of the lipophilic and hydrophilic fractions and whose chemical structure is known. Globally, few *Urtica* species have been screened for their phytochemical composition, with those available so far reporting the presence of sterols, triterpenes, coumarins, phenols, lignans, ceramides, and fatty acids, among other minor compounds, all with a distribution varying in the various organs of the plant. β-sitosterol, transferulic acid, dotriacontane, erucic acid, ursolic acid, scopoletin, rutin, quercetin, and *p*-hydroxybenzyl alcohol are some of the constituents found in *Urtica* species that may be applied for preventive or therapeutic purposes in communicable and non-communicable diseases.[1,2] The main chemical constituents of *U. dioica* are flavonoids, tannins, volatile compounds and fatty acids, polysaccharides, isolectins, sterols, terpenes, protein, vitamins, and minerals.

Conventionally, it is used for the treatment of rheumatism, sciatica, coughs, dandruff, diarrhea, eczema, fever, gout, hemorrhoids, nosebleeds, scurvy, snake bites, tuberculosis, and diabetes which are widespread.[3] Literature evidenced that the plant has been found effective in the treatment of diabetes.[4-7] However, the presence of quercetin makes it suitable herbal drug candidate for diabetic complications, as quercetin is a potent inhibitor of aldose reductase enzyme, which is involved in the pathophysiology of diabetic complications.

Diabetes poses a serious threat to human health as the prolonged hyperglycemia in diabetics is the primary cause of diabetes complications, which include damage and further failure of many organs, including the heart, blood vessels, eyes, kidneys, nerves, and renal function, leading to mortality in diabetics.[8] In diabetics, long-term exposure of the body to excessive glucose concentrations is the main cause of diabetic problems. Increased glucose flow in the polyol pathway occurs during hyperglycemia. Increased polyol pathway activation causes the synthesis of too much sorbitol, which cannot cross biological membranes and accumulates

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Access this article online

Website: http://isfcppharmaspire.com

DOI: 10.56933/Pharmaspire.2023.15133

Date of Submission: 31 July 2023
Date of Revision: 11 August 2023
Date of Acceptance: 16 September 2023

inside cells, causes osmotic stress, and eventually results in chronic diabetic complications [Figure 1].[9-11]

Aldose reductase (AR, ALR2, and AKR1B1) inhibition is the legitimate approach for the management of diabetic complications. However, only single synthetic molecule, namely epalrestat, is available in the market as aldose reductase inhibitors. Conventional medicinal plants are the rich source chemical constituents, thereby can be screened for the identification of natural aldose reductase inhibitors.[12] Curcumin, berberine, and quercetin are well-explored natural aldose reductase inhibitors.[13] In the present research, *in silico* studies on *U. dioica* have been performed against aldose reductase to establish it as a potential candidate for diabetic complications.

MATERIALS AND METHODS

Identification of chemical constituent of *U. dioica*

A total of eight different phytoconstituents [Table 1] of *U. dioica* were identified on the basis of literature for *in silico* studies.

Molecular modeling and energy minimization

The chemical structure of *U. dioica* phytoconstituents was sketched using ChemDraw 8.0. The molecules were subjected to subsequent energy minimization using molecular mechanics and Hamiltonian approximation available in the MOPAC module of Chem3D Ultra 8.0. The geometrical optimization procedure was run till the root-mean-square gradient value reached a value smaller than 0.0001 kcal/mol Å in both the energy minimization methods.

In silico molecular docking studies

For the *in silico* studies, the three-dimensional (3D) crystal structure of aldose reductase was retrieved from Protein Data Bank (RCSB PDB) (PDB Id.: 2FZD). Molegro Virtual Docker (MVD) was used for the preparation and optimization of the target structure.

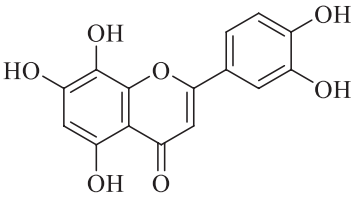
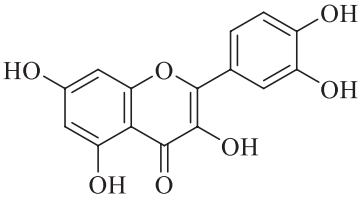
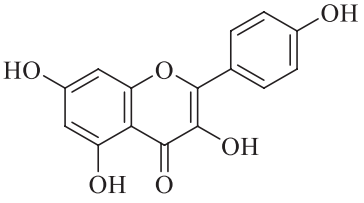
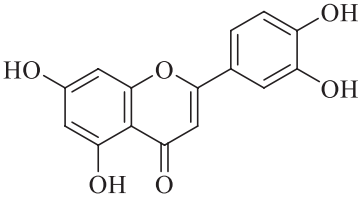
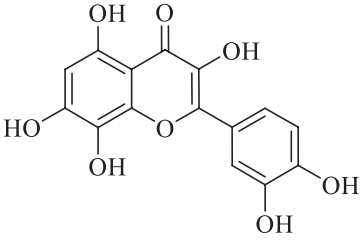
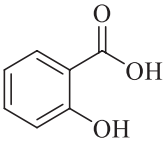
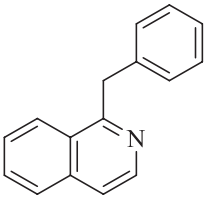
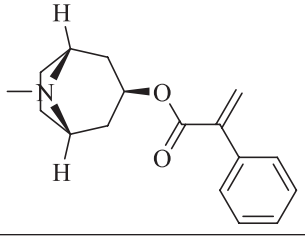
Detection of potential binding cavities

The potential binding sites were mapped within the target aldose reductase by choosing the option "detect cavities" which present in the preparation window of MVD.

Molecular docking

The energy-optimized conformers of molecules were imported into the workspace of MVD. Molecular docking simulations were initiated into the most potent active site (cavity 1) for the estimation of binding affinity and binding mode of interactions of molecules with the target. MolDock

Table 1: Chemical structure of the selected phytoconstituents of the *Urtica dioica*

Compound name	Structure
5,7,8,3',4' -Pentahydroxyflavone	
Quercetin	
Kaempferol	
Luteolin	
Gossypetin	
Salicylic acid	
Benzylisoquinoline	
Apoatropine	

simplex evolution (MolDock SE) search algorithm with a number of runs of 10 and a population size of 50 was selected for performing molecular docking simulations. The pose or conformation of each ligand with the highest MolDock score was selected for the analysis of its binding interactions (H-bond and steric) with the target.

RESULTS AND DISCUSSION

The chemical structure of the selected phytoconstituents of the *U. dioica* for molecular docking is mentioned in Table 1.

MolDock, Re-rank, H-Bond, and Steric scores [Table 2] were obtained as output after the successful accomplishment of molecular docking simulations, different energy functions, such as protein interaction energies, internal ligand energies, and soft penalties, are additively denoted by the MolDock Score. It is the indicator of ligand-target affinity and the best plausible orientation of the ligand within the core of the target. MolDock score uses a piecewise linear potential for the estimation of the steric energy. A weighted combination of the energy terms used by the MolDock score mixed with a few additional terms is

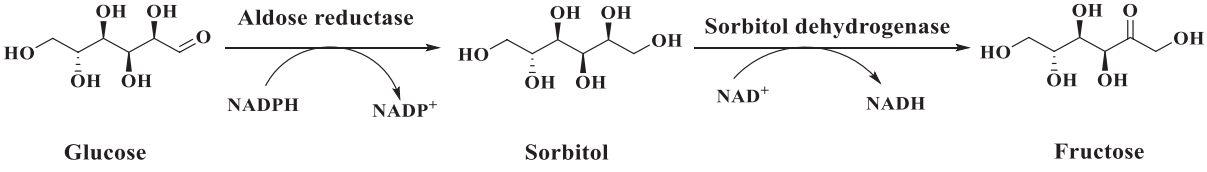


Figure 1: Polyol pathway

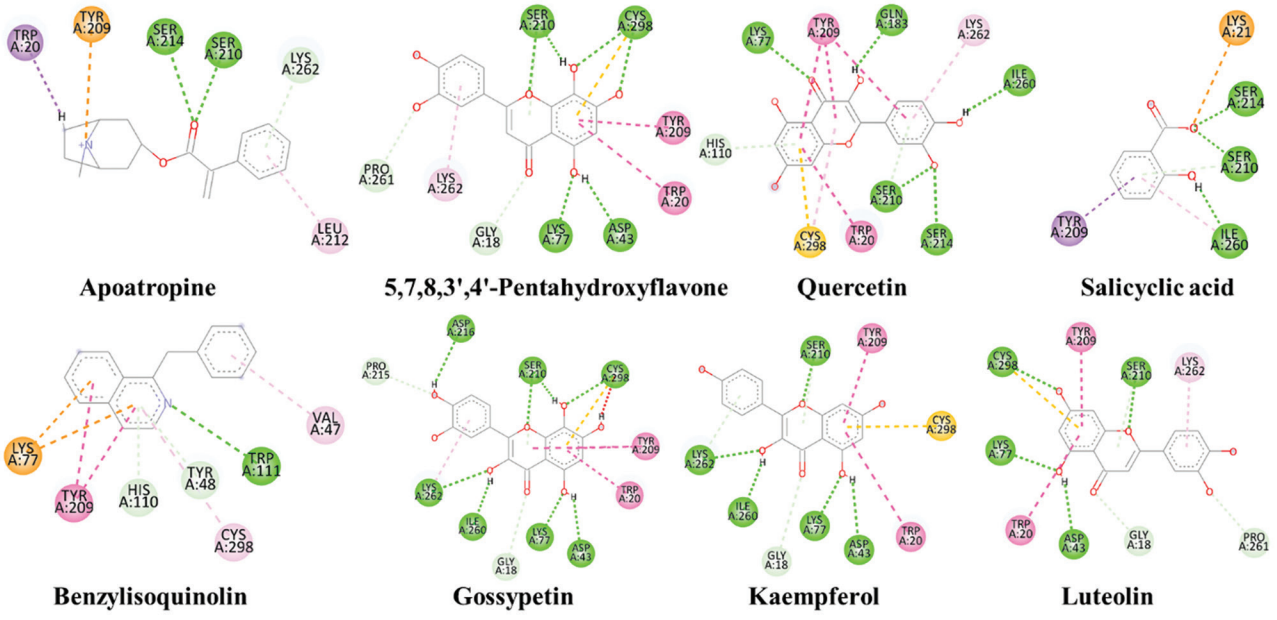


Figure 2: Binding interactions of *Urtica dioica* phytoconstituents

Table 2: Docking scores of phytoconstituent of *Urtica dioica* with AR

Molecule name	Docking scores (in Kcal/mol)			
	MolDock	Re-rank	H-Bond	Steric
Apoatropine	–92.984	–42.625	0.000	–118.401
5,7,8,3',4'-Pentahydroxyflavone	–115.120	–99.562	–8.569	–119.339
Quercetin	–113.456	–63.688	–10.474	–113.851
Salicylic acid	–70.943	–60.275	–7.463	–56.921
Benzylisoquinoline	–91.110	–75.284	0.000	–99.784
Gossypetin	–105.109	–95.916	–9.141	–112.215
Kaempferol	–110.070	–93.399	–6.272	–110.148
Luteolin	–115.767	–87.500	–5.800	–116.729
Epalrestat	–112.759	–62.985	–1.882	–115.391

denoted by the Re-rank score. The accuracy of molecular docking simulations is improved by the Re-rank scoring function. Re-rank scoring function identifies the most probable docking solution after execution of the molecular docking algorithm. Re-rank score includes the steric (by LJ12-6) terms which are Lennard-Jones approximations of the steric energy. H-bond score demonstrates the strength of H-bond interactions between ligand and target. Steric score denotes the bond energies of steric interactions between ligand and aldose reductase.

The binding interactions of *U. dioica* phytoconstituents are presented in Figure 2. 5,7,8,3',4'-pentahydroxyflavone, quercetin, and luteolin showed better docking score compared to reference standard epalrestat. These constituents may impart the aldose reduction inhibition better over the reference standard drug.

CONCLUSION

The *in silico* phytochemical screening signified that 5,7,8,3',4'-pentahydroxyflavone, quercetin, and luteolin which are present in *U. dioica* showed good docking score against aldose reductase. The presence of several flavonoids includes quercetin, in *U. dioica*. Hence, it may be used to treat the imbalance of antioxidants and cure different diabetic complications.

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